

# Dopamine and action potential generation in the axon initial segment

Marco Canepari

### ▶ To cite this version:

Marco Canepari. Dopamine and action potential generation in the axon initial segment. The Journal of Physiology, 2019, 597 (13), pp.3251-3252. 10.1113/JP278217 . hal-02441748

## HAL Id: hal-02441748 https://hal.science/hal-02441748

Submitted on 16 Jan 2020  $\,$ 

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers. L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

### Dopamine and action potential generation in the axon initial segment

#### Marco Canepari<sup>1,2,3</sup>

<sup>1</sup>Univ. Grenoble Alpes, CNRS, LIPhy, F-38000 Grenoble, France. <sup>2</sup>Laboratories of Excellence, Ion Channel Science and Therapeutics, France. <sup>3</sup>Institut National de la Santé et Recherche Médicale, France.

Dopamine is one of the principal neuromodulators in the brain acting on two large families of receptors, namely D1-like and D2-like. It is involved in several important cognitive and motor functions within different brain areas and it is strongly implicated in rewarding and addiction behaviours. In the medial entorhinal cortex (MEC), dopamine is believed to play a crucial role in the spatial cognition functions performed by this area of the brain (Hafting *et al.*, 2005). In particular, type-2 dopamine receptors (D2Rs) appear to be involved in spatial cognition (Mehta *et al.*, 2001) and stellate cells in the MEC contain high levels of D2Rs. Stellate cells in layer II of the MEC are classified as "grid cells" as they provide spatial information to the animal by spanning the environment. The axons of these neurons innervate the hippocampus forming excitatory synapses. Hence, the physiological pathway triggered by D2R activation in MEC stellate cells is likely fundamental for spatial cognition.

A recently published article by Jin et al. (2019) reports novel important findings on the role of dopamine (and in particular of D2Rs) in excitability of stellate cells of the MEC. Dopamine receptors are G-protein coupled receptors (GPCRs) which can regulate the biophysical properties of ion channels and therefore the generation and propagation of the action potential (AP). In this study, the authors first demonstrate that MEC stellate cells direct activation of D2Rs by exogenous application of the agonist bromocriptine, as well as physiological activation of D2Rs by optical stimulation of ChR2 expressed in dopaminergic afferents reduce intrinsic excitability by increasing the threshold for activation of APs. These effects were exclusively mediated by those D2Rs expressed in the stellate cell axon initial segment (AIS). Then, the authors show that the block of T-type voltage-gated Ca<sup>2+</sup> channels (VGCCs) also increases AP threshold preventing the effect of bromocriptine, while D2Rs activation shifts the activation curve of T-type VGCCs in the more positive direction. Finally, while D2Rs and the T-type VGCC subtype Cav3.2 seem to co-localise in the stellate cell AIS, the authors report evidence that the interaction between D2Rs and T-type channels is regulated by protein kinase PKA. The results reported in this study lead to a schematic explanation of the process illustrated in Figure 1. Dopaminergic fibers, arising from the ventral tegmental area and substantia nigra pars compacta (SNc), innervate the MEC and release dopamine that activates D2Rs in the stellate cell AIS. This GPCR acts on T-type VGCCs via a PKA process by shifting the activation profile towards more positive values and, therefore, inhibiting these excitatory channels. This mechanism increases the AP activation threshold and, consequently, decreases cell excitability. This process is also prevented in the presence of high concentrations of the Ca<sup>2+</sup> chelator BAPTA, but whether this Ca<sup>2+</sup> dependence arises at the level of the  $Ca^{2+}$  influx or, more generally, at the level of the  $Ca^{2+}$  homeostasis is still unknown.

Several GPCRs are expressed in the AIS of neurons and this localisation suggests that their function is at the level of AP generation, a phenomenon produced by the synergistic activation of diverse ion channels. This effect is often refereed as "intrinsic neuronal plasticity" of the AP. Thus, the functional regulation of ion channels in the AIS is not peculiar of dopamine receptors. For instance, in another study, it was shown that serotonin acts in the AIS of turtle motoneurons to inhibit voltage-gated Na<sup>+</sup> channels (Cotel *et al.*, 2013), in a manner resembling the regulation of T-type VGCCs by dopamine in the stellate cell AIS. In the case of dopamine, the selective activation of one or the other receptor family (D1-like or D2-like) may lead to an opposite effect like in the case of the axon of pyramidal neurons in prefrontal cortex, where dopamine regulates in two ways the activation of voltage-gated K<sup>+</sup> channels (Yang et al., 2013). In a general manner, the specific activation of a GPCR in the AIS may play a crucial role in the higher function performed by a specific area of the central nervous system by participating to the synergistic system composed by different ion channels that generates the AP. In the case of dopamine, the mechanisms characterised in the present study are involved in MEC stellate cell information processing, may contribute to spatial cognition and may possibly occur in other hippocampal and cortical regions innervated by dopaminergic fibers.



### Figure 1. Dopamine affect in the MEC stellate cell AIS

Dopamine activates D2Rs that shifts the activation curve of T-type VGCCs in the more positive direction inhibiting this channels and decreasing neuronal excitability. This interaction is regulated by PKA.

#### REFERENCES

Cotel F, Exley R, Cragg SJ & Perrier JF (2013) Serotonin spillover onto the axon initial segment of motoneurons induces central fatigue by inhibiting action potential initiation. *Proc Natl Acad Sci U S A* **110**, 4774-4779.

Hafting T, Fyhn M, Molden S, Moser MB & Moser EI (2005) Microstructure of a spatial map in the entorhinal cortex. *Nature* **436**, 801-806.

Jin X, Chen Q, Song Y, Zheng J, Xiao K, Shao S, Fu Z, Yi M, Yang Y, Huang Z. (2019). Dopamine D2 receptors regulate the action potential threshold by modulating T-type calcium channels in stellate cells of the medial entorhinal cortex. *J Physiol (Lond)* in press.

Mehta MA, Swainson R, Ogilvie AD, Sahakian J & Robbins TW (2001) Improved short-term spatial memory but impaired reversal learning following the dopamine D(2) agonist bromocriptine in human volunteers. *Psychopharmacology (Berl)* **159**, 10-20.

Yang J, Ye M, Tian C, Yang M, Wang Y & Shu Y (2013) Dopaminergic modulation of axonal potassium channels and action potential waveform in pyramidal neurons of prefrontal cortex. *J Physiol* **591**, 3233-3251.